REMARKS

Reconsideration of this application is respectfully requested.

Following entry of this Amendment, claims 1-6, 8-12, 14-25 and 50 will be pending. Claim 1 is amended. Claims 7 and 13 have been cancelled because the amendment to Claim 1 renders them redundant. Claims 29-49 have been cancelled by this paper. Applicants reserve the right to pursue the subject matter of these cancelled claims and all previously cancelled claims in a divisional application.

REJECTION UNDER 35 U.S.C. §103

Claims 1-12, 14-20, 22-24, 29-40, 42-48, and 50 stand rejected under 35 U.S.C. §103 over the combination of Ullrich in view Hexdall (1999) *Strategies* vol 12, issue 2, Shibuya and Murata. Claims 29-49 have been cancelled to expedite the allowance of the remaining claims.

For the reasons given below, Applicants respectfully assert that the instant invention would not have been obvious to one skilled in the art, in the combination of Ullrich in view Hexdall, Shibuya and Murata. These references do not disclose a method for determining VEGF activity in a sample or for a cell line useful in such a method. There was no motivation in any of Ullrich, Hexdall, Shibuya or Murata to combine the teaching of these references. Even if there were motivation to combine the references there would not have been a reasonable expectation of success.

MPEP section 706.02(j) states that in order to establish a prima facie case of obviousness, three basic criteria must be met.

1. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

2. There must be a reasonable expectation of success.

3. The prior art references must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and **not** based on applicant's disclosure. MPEP section 706.02(j) (emphasis added).

The Examiner states that "the rejection relies solely on Ullrich and Hexdall to teach all the limitations of the claims and to provide motivation to combine the two teachings." The Examiner further states the "teachings of Shibuya *et al.* and Murata *et al.* are cited merely as evidence that the skilled artisan would have known, at the time the instant application was filed, that MAP kinase activation and phosphorylation of ELK-1 are features of signal transduction through the FLK-1 VEGF receptor."

The present invention relates to methods of determining the amount of bioactive VEGF in a sample and to a cell line useful in such a method. The claims have been amended to recite that the methods of the invention employ phosphorylatable protein that can be phosphorylated by MAPK. Applicants respectfully submit that the references do not adequately teach or suggest this invention.

The disclosure in Ullrich relates to Flk-1 and the use of ligands for Flk-1 to modulate angiogenesis and vasculogenesis. Ullrich is focused on using Flk-1 to identify compounds that are VEGF agonists or antagonist. There is no suggestion that one would need to add the other elements recited in the present invention. Moreover, there is no teaching or suggestion in Ullrich that Flk-1 could be used in an assay to determine the amount of VEFG activity in a sample or that such an assay would be desirable. In short, Ullrich does not provide motivation to combine the disclosure of Ullrich with Hexdall.

There in nothing in Hexdall that overcomes the deficiency of Ullrich. Hexdall is directed to cell lines that are "for studying signal transduction pathways that converge at the transcription factors CREB, Elk1 and c-Jun." (p. 1) Hexdall indicates that the "potential applications of these cells lines include studying signal transduction and transcription mechanisms and assessing protein-protein interactions in mammalian cells." (p 1). Hexdall also notes that "[a]nother application for these cells includes adaptation for high-throughput drug screenings, since many components of signal transduction pathways are potential targets for drug development efforts." (p. 2).

The current invention relates to methods of determining the amount of bioactive VEGF in a sample. Hexdall does not suggest VEGF related assays, and does not teach or suggest that an assay to quantify bioactive VEGF could be obtained or would be desirable. There is no

suggestion to transfect the cells described in Hexdall with a VEGF receptor, much less that such cells would have the beneficial properties taught in applicants' specification.

Even if there were motivation to combine, the references do not provide a reasonable expectation that the combination of a VEFG receptor expression vector, a chimeric transactivation vector and a reporter vector as described in the instant invention would be useful in the determination of the VEFG activity in a sample. The references indicate that efficiency of signaling using the described elements in different cells lines is not predictable. For example, Shibuya et al teach that the PLCγ-PKC-Raf-MEK-MAP kinase pathway towards DNA synthesis is activated more efficiently in primary endothelial cells than in NIH3T3 cells (p. 28). Further, as noted by Murata, the "downstream signal pathway(s) of VEGF has not been well understood" (p. 388). Murata describes the components of this signaling cascade in cells that endogenously express these components. Murata does provide any indication that HeLa cells transformed with VEGF receptor, a chimeric transactivator vector and a reporter vector form an efficient assay system that would be suitable for determination of the VEFG activity in a sample. Rather, Murata demonstrates the complexity of the signaling pathway.

In summary, none of the cited references would have provided a motivation to combine or a reasonable expectation of success. In the absence of such teachings, it is respectfully submitted that the present claims are patentable over the cited combination. Therefore, withdrawal of the rejection of claims 1-6, 8-12, 14-20, 22-24 and 50 under 35 U.S.C. §103 over the combination of Ullrich in view Hexdall, Shibuya and Murata is respectfully requested.

Claims 22 and 23 are rejected under 35 U.S.C. §103 as unpatentable over the combination of Ullrich in view of Hexdall and Wen.

Claim 22 is submitted to be patentable over the combination for the reasons described above with respect to the first rejection.

Claim 23 is respectfully submitted to be separately patentable. While Wen teaches activation of VEGF receptor within the claimed range of VEGF concentration, it nowhere teaches that such activation is sufficient in HeLa cells transformed with a VEGF receptor and the other recited elements to produce an assay that is efficiently used to determine the VEFG activity in a sample, as described in the present application. Mere activation of Flk-1 would not have necessarily resulted in the efficient generation of signal required for a particularly useful assay, as described by applicants.

Withdrawal is requested of the rejection of claims 22 and 23 under 35 U.S.C. §103 as unpatentable over the combination of Ullrich in view of Hexdall and Wen

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-12, 14-25, 29-40 and 42-49 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The primary basis for the rejection appears to be that the claims relate to a chimeric tranactivator that should be limited to GAL4-ELK-1 fusion.

Applicants submit that the presently amended claims, which recite that the phosphorylatable protein can be phosphorylated by MAPK, are appropriately limited. In particular, use of other chimeric transactivators would not be expected to result in loss of the benefits of the invention, i.e., substitution of another appropriate chimeric transactivator would not be expected to disrupt the signaling chain. It is respectfully submitted that the present claims are sufficiently limited. Therefore, the rejections of Claims 1-6, 8-12, and 14-25 under 35 USC §112, first paragraph are improper and should be withdrawn.

CONCLUSION

Applicants respectfully request reconsideration and withdrawal of all of the rejections in light of the amendments and remarks made herein and allowance of all the pending claims. This application is submitted to now be in condition for allowance. Issuance of a notice to that effect is respectfully requested.

Respectfully submitted,

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Cynthia M. Bott
Registration No. 46,568
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (734) 622-4476
Fax (734) 622-1553